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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
11/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	09/809,029	BARNARDO ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____ .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/01/10 has been entered.

Specification

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). In the instant application, the claims submitted 09/01/10 lists claims 1-46 as being cancelled. However, the previous claims filed 11/30/09 only listed claims 1-42. Therefore, it appears that claims 43-46 never existed or were never submitted in a listing of claims. Thus, claims 43-46 could not have been cancelled. Also, there are no claims 64 & 65. The current list of claims provides for claims 1-63 and 66-72 and fails to provide clear indication of claims 43-46 or list claims numbered 64 & 65 in the current claims submitted 09/01/10.

Misnumbered claims 47-72 have been renumbered 43-66.

NOTE: In the event applicant files an amendment in the Application. Applicant is required to provide a correct numbered listing of the claims.

Currently, claims 43-66 are pending and under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 43-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46, line 7 the recitation "of antibodies" is vague and indefinite because it is unclear if Applicant is referring to the antibodies recited in the preamble of the claim or if Applicant intends some other antibodies.

Claim 62, line 8 the recitation "of antibodies" is vague and indefinite because it is unclear if Applicant is referring to the antibodies recited in the preamble of the claim or if Applicant intends some other antibodies.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 43-52, 54, 55, and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty (US 5,292,641) in view of Tidey et al (US 6,046,013) and further in view of Chang et al (US 5,270,169) and Walter et al. (International Immunology, Vol. 9, p. 451-459, 1997).

Pouletty disclose a method of detecting and identifying antibodies to HLA alleles (antigens, as indicated on page 5 of the remarks section filed by Applicant 09/01/10). bound (immobilized) to a support (e.g. abstract, col 1- col3). Pouletty discloses that the

method can be used to detect antibodies to the alleles of interest (col 3). Pouletty discloses that the HLA allele of interest can be Class I or Class II (col 3). Pouletty discloses that the antigens can be derived from any convenient source of the desired antigen repertoire (col 3, lines 22-30). Pouletty disclose contacting a sample such as serum, plasma, saliva, or cerebrospinal fluid (body fluids) to detect the antibodies in the sample (e.g. col 2 – col 4). Pouletty et al disclose that the detection of antibody bound to the HLA antigen can be determined by utilizing a labeled antibody (col 4, lines 37-68). Pouletty discloses that the label can be enzymes, radioisotopes, biotin to bind to labeled avidin (col 4). Pouletty also discloses that the detection can be by ELISA, FIA or RIA (col 4). Pouletty discloses that a panel of HLA antigens can be used to detect the antibodies (e.g. col 2) and that a repertoire of antigens can be used (col 3). Pouletty discloses that the reagents can be packaged into a kit (col 5). Pouletty discloses that the support can be a bead, microtiter plate or nitrocellulose (col 3). Pouletty et al disclose the assay can take less than three hours (col 6, lines 13-40).

Pouletty et al differs from the instant invention in failing to specifically teach the HLA antigens are immobilized to discrete sites of the solid support.

Tidey et al discloses methods for detecting and identifying antibodies in a sample (e.g. abstract, col 2). Tidey et al discloses that HLA antigens which are unique from each other and separated from each other on a solid support are used to detect the antibodies (e.g. col 2 - col 4). Tidey et al discloses that HLA antigens can have specific alleles which bind to antibodies (e.g. col 4). Tidey et al discloses that 40 different HLA molecules can be immobilized to the solid support at different locations (col 4, lines 65-

67). Tidey et al discloses that the separation of different HLA molecules provides for an infinite number of grades of antibody reactions which can be assigned, making it much easier to sort and identify the antibodies (e.g. col 12) and also teaches that it provides alternative techniques which can be performed simply, can be automated, provides a readily discernible result which is significant for the prognosis of transplant acceptance, and are comparable to data from existing tests. (col 2, lines 23-27). Tidey et al also discloses packaging components into a kit.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate different HLA alleles (antigens) at separate locations of the support of Pouletty because Pouletty specifically teaches that a panel of alleles (antigens) can be used and Tidey et al shows that using different HLA antigens at different locations of a support provides for an infinite number of grades of antibody reactions which can be assigned, making it much easier to sort and identify the antibodies and also teaches that it provides alternative techniques which can be performed simply, can be automated, provides a readily discernible result which is significant for the prognosis of transplant acceptance, and are comparable to data from existing tests.

Pouletty and Tidey et al fail to teach the use of recombinant MHC or HLA molecules.

Chang et al teaches that it is known in the art that synthetic HLA antigens which mimic the antigenic reactivity of HLA epitopes are equivalent to HLA antigens for the detection of specific antibodies in a biological sample (col 3, lines 48-62). Chang et al

teaches that the detection of the antibodies can be of antibodies to at least one HLA allele (col 2, lines 15-20). Chang et al also teaches HLA molecules can be attached to solid supports such as a microtiter plate, beads or nitrocellulose (col 3, lines 1-19).

Walter et al discloses that recombinant HLA molecules can be used to detect antibodies in a sample and teaches the production of recombinant HLA molecules. Walter et al., disclose detecting a monoclonal PA2.1 antibodies (specific for HLA-A2 and A28). Walter et al disclose that this antibody binds to recombinant HLA-A2 peptide complexes. Walter et al disclose detecting the PA2.1 antibodies bound to the A2 complex with goat anti-mouse Ig conjugated to horseradish peroxidase (p. 452). Walter et al disclose that the HLA-A2 molecule is produced in E.Coli (prokaryotic expression system) (p. 451). Walter et al disclose the recombinant molecule can be immobilized and bound by antibody (p. 456, first column, lines 43 – 53). Walter et al teaches the use of two different peptides to form the recombinant complexes (e.g. p. 451, 2nd col). Walter et al disclose assembling the HLA-A2 (HLA-A*0201) heavy chain and B_2-microglobuling in the presence of a peptide derived from HIV-1: a peptide from reverse transcriptase (RT-IV9, amino acids 476-484, ILKEPVHGV) and a peptide from gag protein (Gag, amino acids 77086, SLYNTVATL) (It is noted that this recombinant molecule appears to be the same recombinant molecule as disclosed by applicant (see page 23, Table 1). Walter et al disclose labeled antibodies that bind to the PA2.1 antibodies. Walter et al teaches that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes (p.456, 2nd col).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the production of recombinant HLA antigens and the HLA antigens such as taught by Walter et al into the modified method of Pouletty because Chang et al teaches that it is known in the art of detecting HLA antibodies that a synthetic HLA antigen can be substituted as an equivalent reagent for HLA antigens for the purpose of detecting HLA antibodies and Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes.

With respect to claims 47 and 51 as currently recited, the combination of references teach that the recombinant molecules can be produced in prokaryotic cells. Therefore, as disclosed by Applicant on page 12 of the current specification it will be understood by those skilled in the art that the MHC molecule will be synthesized in an un-glycosylated form.

With respect to the number of MHC antigens represented as currently recited claims 60 and 61. The optimum number of MHC antigens to be represented can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a

process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

9. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty, Tidey et al., Chang et al., and Walter et al., as applied to claims 43-52, 54, 55, and 57-61 above, and further in view of Luxembourg et al.

See above for the teachings of Pouletty, Tidey et al., Chang et al., and Walter et al.

Pouletty, Tidey et al., Chang et al., and Walter et al. differ from the instant invention in failing to teach the heavy chain is fused to biotin.

Luxembourg et al disclose recombinant MHC molecules which are biotinylated (page 3, paragraph 0018, & page 4, paragraph 0027). Luxembourg et al disclose that these recombinant MHC molecules are biotinlyated to provide attachment to solid support coated with avidin. Luxemburg et al disclose that the use of this avidin-biotin system provides for the isolation of peptides such as antibodies (p. 5, paragraphs 0030, and 0031).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an avidin-biotin system as taught by Luxembourg et al into the modified method of Pouletty because Luxembourg et al shows that the use of this avidin-biotin system provides for the isolation of peptides such as antibodies. Further, the use of avidin-biotin systems to immobilize and capture reagents is very well

known in the art. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating avidin-biotin as taught by Luxembourg et al into the modified method of Pouletty.

10. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty, Tidey et al., Chang et al., and Walter et al as applied to claims 43-52, 54, 55, and 57-61 above, and further in view of Ollington et al (US 5,403,745).

See above for the teachings of Pouletty, Tidey et al., Chang et al., and Walter et al.

Pouletty, Tidey et al., Chang et al., and Walter et al differ from the instant invention in failing to teach the sample is purified plasma.

Ollington et al disclose methods of determining an analyte in a biological fluid such as plasma or serum (e.g. abstract, col 5-7, col 11). Ollington et al disclose that the analyte can be immunoglobulins in the presence of non-targeted or interfering immunoglobulins (e.g. abstract, col 5) and teaches the purification of the sample to remove the non-targeted or interfering immunoglobulins (e.g. col 5, col 15-16). Ollington et al discloses that the purification of an analyte in the sample permits the enhancement of the efficiency of existing routine diagnostic tests currently in clinical use (e.g. col 6, lines 65-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate purification steps such as taught by Ollington et al into the modified method of Pouletty et al because Ollington et al teaches that the

purification of an analyte in the sample permits the enhancement of the efficiency of existing routine diagnostic tests currently in clinical use.

11. Claims 62-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pouletty, Tidey et al., Chang et al., and Walter et al as applied to claims 43-52, 54, 55, and 57-61 above, and further in view of Boguslaski et al (US 5,420,016).

See above for the teachings of Pouletty, Tidey et al., Chang et al., and Walter et al.

Pouletty, Tidey et al., Chang et al., and Walter et al differ from the instant invention in failing to teach all of the components packaged into a kit.

Boguslaski et al disclose assembling various system components into a test kit. By assembling these components into test kits, it makes it more convenient and facile for the test operator (col 7, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to assemble the various components of the modified method of Pouletty into kits such as taught by Boguslaski et al because Pouletty teaches the use of kits and Boguslaski shows that test kits make it more convenient and facile for the test operator. Therefore, one of ordinary skill in the art would have been motivated to include the components of the modified method of Pouletty into a kit.

Response to Arguments

12. Applicant's arguments filed 09/01/10 have been fully considered but they are not persuasive.

Applicant argues that the Tidey reference does not teach immobilization of individual HLA molecules per se to discrete site on a solid support as instantly claimed. Applicant argues that Tidey suggest the use of HLA molecule representing an individual's signature (e.g. a "grouping" or preparation" of multiple HLA molecules), and not individual HLA molecules as instantly claimed.

These arguments are not found persuasive because the Examiner has not relied upon Tidey for the individual molecules but rather has relied upon Tidey et al for teaching that it is known in the art to have unique antigens at different sites for the detection of HLA antibodies. As discussed supra and in the previous office action Pouletty et al specifically teaches the use of a repertoire of antigens and specifically teaches that a panel of alleles (antigens) can be used and Tidey et al shows that using different HLA antigens at different locations of a support provides for an infinite number of grades of antibody reactions which can be assigned, making it much easier to sort and identify the antibodies and also teaches that it provides alternative techniques which can be performed simply, can be automated, provides a readily discernible result which is significant for the prognosis of transplant acceptance, and are comparable to data from existing tests. Thus, one of ordinary skill in the art would be motivated to provide a repertoire of unique alleles at different sites in the method of Pouletty et al to provide for a method of detecting and identifying antibodies to HLA alleles of interest.

Applicant states that it may be correct that Walter's data shows that the mouse mAb PA2.1 being "specific for HLA-A2 and A28", bind the recombinant HLA complexes produced therein. Applicant argues that Walter's descriptions are not suggestive or

even relevant to the detection of antibodies present "in a body fluid sample as instantly claimed. Applicant states that the skilled artisan would understand that there is a significant difference between the binding of a purified monoclonal antibody to a recombinant HLA molecule and the detection of a particular antibody present "in a body fluid sample" and that the skilled artisan would understand that the binding of a mouse mAb to a recombinant HLA molecule would have little, if any, predictive value regarding the instantly recited claims. Applicant further states that Walter is using a highly purified preparation of mouse mAb that is not even specific for a single type of HLA antigen.

These arguments and statements are not found persuasive because (1) Applicant is reminded that 103 rejections are based on one of ordinary skill in the art and not the skilled artisan. (2) Further, for reasons stated above and in the previous office action, that the combination of references read on the instantly recited claims and that it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the production of recombinant HLA antigens and the HLA antigens such as taught by Walter et al into the modified method of Pouletty because Chang et al teaches that it is known in the art of detecting HLA antibodies that a synthetic HLA antigen can be substituted as an equivalent reagent for HLA antigens for the purpose of detecting HLA antibodies and Walter shows that recombinant HLA antigens can be used to detect allele specific antibodies and that the recombinant complexes contain native epitopes, consistent with the presence of correctly folded molecular complexes.

With respect to Applicant's statement that Walter is using a highly purified preparation of mouse mAb that is not even specific for a single type of HLA antigen. This argument is not found persuasive because the Examiner has not relied upon Walter for the mouse mAb but rather has relied upon Walter et al for teaching that it is known in the art to produce recombinant HLA molecules and that recombinant molecules bind to antibodies. Further, it appears that Applicant is arguing Walter et al individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For the reasons stated above the combination of Pouletty (US 5,292,641) in view of Tidey et al (US 6,046,013) and further in view of Chang et al (US 5,270,169) and Walter et al. (International Immunology, Vol. 9, p. 451-459, 1997) reads on the instantly recited claims.

Conclusion

13. No claims are allowed.

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Degen et al (US 4,693,985) teaches a method for the separation and/or concentration of ligands, both wanted and unwanted from biological fluids such as plasma (col 3).

Arguello et al., Proc Natl. Acad. Sci. USA, Vol 93, 1996, pgs 10961-10965) teaches different HLA class I alleles (e.g Table 2, page 10962).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/Melanie Yu/
Primary Examiner, Art Unit 1641